Exhibit A

USPTO PATENT FULL-TEXT AND IMAGE DATABASE

Searching 1976 to present...

Results of Search in 1976 to present db for:
ACLM/"electron withdrawing group": 929 patents.
*Hits **1** through **50** out of **929***

Next 50 Hits

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Refine Search ACLM/"electron withdrawing group"

	PAT. NO.	Title
1	6,593,334	Camptothecin-taxoid conjugates as antimitotic and antitumor agents
2	6,593,069	Photothermographic material and method for forming images
3	6,590,009	Polymerization and/or crosslinking method under electron beam and/or gamma radiation
4	6,586,555	Processes of preparing condensed polymers with polycarboxylic acids and polyamines
5	6,586,356	Catalyst component for addition polymerization, catalyst for addition polymerization, and process for producing addition polymer
6	6,584,266	Chromophores for polymeric thin films and optical waveguides and devices comprising the same
7	6,582,898	Silver salt photothermographic material
8	6,582,896	Photothermographic material
9	6,576,779	Catalyst compositions and processes for olefin polymers and copolymers
10	6,569,612	Photographic element containing a high-dye-yield coupler for producing a yellow hue
11	6,566,508	Fluorogenic compounds and uses therefor
12	6,566,320	Bleaching composition containing chromotropic compound
13	6,566,059	Method for analyzing polynucleotides
14	6,562,910	Trifunctional olefinic-capped polymers and compositions that include such polymers
15	6,562,844	Oxazolidinone combinatorial libraries, compositions and methods of preparation
16	6,562,181	Reactive adhesives and coatings with trifunctional olefinic monomers
17	6,559,323	Process for the preparation of an oxirane, aziridine or cyclopropane
18	6,559,261	Polymer production

19 6,558,956 Method and apparatus for detection of a controlled substance
20 6,558,893 Photographic material having improved color reproduction
21 6,558,890 Imaging element containing a blocked photographically useful compound activated by azolesulfonyl-assisted 1,2-elimination
22 6,558,888 Imaging materials containing novel benzothiazine dyes
23 6,555,959 Material for light emitting device, light emitting device using thereof, and amine compound
24 6,554,948 Process for improving the adhesion of polymeric materials to metal surfaces
25 6,551,467 Microwave facilitated allyllic substitution
26 6,548,240 Photothermographic material
27 RE38,073 Products for peptide coupling
28 6,541,674 Process for the condensation of a carbonyl compound with an aromatic derivative in a basic medium
29 6,541,647 Methods of synthesis of substituted tetrahydrofuran compound
30 6,537,712 Color photothermographic elements comprising blocked developing agents
31 6,531,470 Oxazolidinone combinatorial libraries, compositions and methods of preparation
32 6,528,596 Modified particles, catalyst for olefin polymerization, and process of producing olefin polymer
33 6,528,227 Film/screen system and image-forming system for use in direct X-ray applications
34 6,521,619 Aryl phenylcyclopropyl sulfide derivatives and their use as cell adhesion inhibiting anti-inflammatory and immune suppressive agents
35 6,521,397 Photographic element containing azole couplers
36 6,521,389 Silver halide photographic light-sensitive material and processing method thereof
37 6,515,078 Trifunctional olefinic-capped polymers and compositions that include such polymers
38 6,512,043 Two-part structural adhesive having long working time
39 6,509,495 Selective hydrodehalogenation method
40 6,509,346 Chemokine receptor antagonists and methods of use therefor
41 6,506,844 Trifunctional olefinic-capped polymers and compositions that include such polymers
42 6,506,704 Olefin polymerization catalysts and processes for making and using same
43 6,506,528 Photothermographic element containing a mixture of blocked developers
44 6,503,926 Chemokine receptor antagonists and methods of use therefor
45 6,503,697 Light-sensitive silver halide photographic material for forming direct-positive images and method for making same
46 6,503,566 Process for improving the adhesion of polymeric materials to metal surfaces
47 6,503,432 Process for forming multilayer articles by melt extrusion
48 6,500,980 Process for preparing amino derivatives of C-H-acid compounds
49 6,500,590 Dual process compatible color photothermographic element comprising dry thermal development
50 6,500,545 Aminoplast-based crosslinkers and powder coating compositions containing such crosslinkers

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United States Patent **5,939,346**
Marks , et al. **August 17, 1999**

Catalyst system comprising an aryloxyaluminoxane containing an electron withdrawing group

Abstract

Aryloxyaluminoxanes containing the unit ##STR1## where R is unsubstituted or substituted aryl, such as phenyl or naphthyl, are useful as a cocatalysts in Ziegler-Natta and Kaminsky-type olefin polymerization catalysts. They can be formed by reaction of a source of water with an organoaluminum compound containing the desired aryloxy moiety or by reaction of preformed aluminoxane with an organic compound, such as a phenol, containing such a moiety.

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Filed: **October 6, 1993**

Current U.S. Class: **502/103**; 502/117; 502/125

Intern'l Class: B01J 031/14

Field of Search: 502/103,117,125

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Primary Examiner: Griffin; Walter D.
Attorney, Agent or Firm: Fennelly; Richard P.

Parent Case Text

This is a continuation of application Ser. No. 07/969,920 filed Nov. 2, 1992, now U.S. Pat. No. 5,391,793.

Claims

We claim:

1. A Ziegler-Natta or Kaminsky catalyst system for the polymerization of olefins which comprises, as a cocatalyst, a composition of matter which predominantly comprises aryloxyaluminoxane containing at least one ***electron withdrawing group***.

2. A catalyst system as claimed in claim 1 wherein the composition of matter predominantly comprises phenoxyaluminoxane containing at least one ***electron withdrawing group***.

3. A catalyst system as claimed in claim 2 wherein the electron withdrawing group is halogen.

4. A catalyst system as claimed in claim 3 wherein the halogen is fluoro.

5. A catalyst system as claimed in claim 3 wherein the halogen is chloro.

Description

BACKGROUND OF THE INVENTION

Aluminoxanes, for example, those of the general formula --(O--AlR).sub.n --, where R is an alkyl group, such as methyl, have received considerable attention in recent years due to their ability to form active olefin polymerization catalysts when combined with Group IV metallocenes. Among these, the most important aluminoxane is methylaluminoxane (R=methyl) since it produces the highest activity catalysts. Methylaluminoxane, however, is expensive since its synthesis requires the use of a rather expensive trimethylaluminum reagent. Furthermore, trimethylaluminum is very air- and moisture-sensitive and such factors make them less desirable for large scale industrial applications.

The disclosures in the art which cover aluminoxane compositions where R, as described above, can be selected from alkyl or, in some cases, aryl, all call for direct bonding of the R group to the aluminum atom. Examples of such disclosures include the following: U.S. Pat. No. 3,242,099 (R=C.sub.1 -C.sub.12 alkyl or aryl); U.S. Pat. No. 4,404,344 (R=C.sub.1 -C.sub.5 alkyl); U.S. Pat. No. 4,544,762 (R=C.sub.1 -C.sub.6 alkyl); U.S. Pat. No. 4,665,208 (R=C.sub.1 -C.sub.8 alkyl); U.S. Pat. No. 4,874,880 (R=hydrocarbyl such as C.sub.1 -C.sub.4 alkyl); U.S. Pat. No. 5,041,584 (R=C.sub.2 or higher alkyl); and European Patent Publication No. 324,856 (R=other than n-alkyl such as branched alkyl, cycloalkyl, or aryl).

U.S. Pat. Ser. No. 5,329,032, describes the manufacture of polymethylaluminoxane compositions of enhanced solution stability by reaction of the polymethylaluminoxane with certain organic compounds containing heteroatoms such as oxygen. Included as possible compounds are benzyl alcohol, nonyl phenol and butylated hydroxy toluene. The amount of such an organic compound is said to be no more than about 15 wt % of the polyaluminoxane, preferably up to about 10 wt %. Therefore, the resulting compositions, if an aryloxy-containing compound were selected, would contain a minor amount of aryloxy moieties.

SUMMARY OF THE INVENTION

The present invention relates to aryloxyaluminoxanes where an unsubstituted or substituted aryloxy group is directly bonded to the aluminum atom of an aluminoxane so that a predominant amount of aryloxy moieties, such as those comprising an --OC.sub.6 H.sub.5 structure, are a substituent on aluminum.

DETAILED DESCRIPTION OF THE INVENTION

The term "aryloxyaluminoxane" as used herein is to be construed as covering aluminoxane compositions which are linear or cyclic and which contain the unit ##STR2## where n can be an integer of 2 or more and R is an unsubstituted or substituted aryl, such as a phenyl group or a naphthyl group. The phenyl group (R) is preferred and can contain at least one suitable electron withdrawing group such as halogen (fluoro, bromo, chloro, or iodo), nitro, trifluoromethyl, cyano, --C(O)R', where R' is alkyl, --C(O)OR", where R" is alkyl, aryl, and the like. A preferred selection for R is pentafluorophenyl. Alternatively, R can be substituted with such electron donating groups as alkyl, alkoxy, or aryloxy. The alkyl group(s) can be straight chain or branched and can contain from one to twelve carbon atoms.

The terminology "predominant", and grammatical variants, is intended to distinguish the present materials from those polymethylaluminoxanes described in U.S. Pat. Ser. No. 853,466 which contain relatively low amounts of aryloxy groups in certain embodiments (i.e., under about 15 wt %). In the compositions of the present invention a major amount of the aluminum atoms contain aryloxy substituents, preferably about 50% to substantially about 100%.

It is deemed that linear aluminoxanes in accordance with the present invention have the structure ##STR3## while cyclic aluminoxanes have the predominant structure

›Al(OR)O!.sub.n+2

where R is unsubstituted or substituted aryl, such as phenyl, as described above, and R' can be lower alkyl, such as methyl, or hydroxyl. Both cyclic and acyclic (linear) structures can be present in the aluminoxane product.

The aryloxyaluminoxanes of this invention can be formed by reacting an organoaluminum compound containing the aryloxy group, for example, of the formula R.sub.2 AlOR', where R can be alkyl, for example, one containing from one to about eight carbon atoms, such as methyl and R' is unsubstituted or substituted aryl, with a source of water, such as liquid water or a compound, such as copper or sodium sulfate having water of crystallization, or silica or alumina, having water of absorption, which can supply the water.

An alternative way to make the aryloxyaluminoxanes of this invention is to react a conventional aluminoxane, such as methylaluminoxane with a reactive compound containing the desired unsubstituted or substituted aryloxy group, preferably a phenol.

The aryloxyaluminoxanes of this invention all have utility as cocatalysts for olefin polymerization in Ziegler-Natta and Kaminsky-type catalyst systems based on such catalyst components as unsupported titanium trichloride, supported titanium with and without donor, cyclopentadienyl titanium chlorides, and cyclopentadienyl and substituted cyclopentadienyl zirconium chlorides and alkyls. The Kaminsky-type systems are preferred. Suitable examples of these preferred systems include zirconocene dichloride,

zirconocene dimethyl, bis(pentamethylcyclopentadienyl) dichloride or dimethyl, bis(indenyl) dimethyl, 2,2'-dimethylsila-bis(cyclopentadienyl) zirconium dimethyl, and the like. Still more examples of suitable catalyst components containing either zirconium or hafnium are presented in W. Kaminsky, Shokubai, 33, 536 (1991) and J. A. Swen et al., Makromol. Chem., Makromol. Symp., 48/49, 253-295 (1991).

The present invention is further illustrated by the following Examples.

EXAMPLE 1

This Example illustrates synthesis of a phenoxy-aluminoxane.

A solution of 1.2 g of Me.sub.2 AlOC.sub.6 F.sub.5 (D. G. Hendershot et al., Organometallics, 1991, 10, 1917-1922) in toluene was slowly added to a toluene solution which contained CuSO.sub.4.5H.sub.2 O (0.4 g, 5 equivalents of OH) at -40.degree. C. The mixture was raised to room temperature over a period of two days with stirring. It was then filtered through a glass frit, and the toluene was removed under vacuum. A white solid was obtained in high yield. The .sup.1 H NMR spectrum of this solid product in C.sub.6 D.sub.6 showed no Al--CH.sub.3 resonances. The .sup.19 F NMR spectrum clearly revealed the presence of --OC.sub.6 F.sub.5 groups.

EXAMPLE 2

This Example illustrates the use of the product from Example 1 as a cocatalyst in the polymerization of ethylene.

Fifteen milligrams of Cp'.sub.2 ZrMe.sub.2 (Cp'=.eta..sup.5 -C.sub.5 Me.sub.5) was mixed with 100 mg of the white solid obtained from Example 1 (Al/Zr=11) in 50 mL of dry toluene to yield a homogeneous solution. The solution was then exposed to ethylene (one atmosphere) for fifteen minutes with rapid stirring. After quenching the reaction with methanol, filtering, washing, and drying, 2.0 g of solid polyethylene was obtained.

EXAMPLE 3

This Example illustrates the use of the product from Example 1 as a cocatalyst in the polymerization of propylene.

Six milligrams of Cp'.sub.2 ZrMe.sub.2 (Cp'=.eta..sup.5 -C.sub.1 Me.sub.5) and 12 mg of the white solid obtained from Example 1 (Al/Zr =3.5) were mixed in a quartz pressure tube. Then, 4 mL of dry toluene and 10 mL of liquid propylene were condensed into the above tube at -78.degree. C. The reaction mixture was stirred at 0.degree. C. for one hour and then at room temperature for fifty minutes. The reaction was quenched with methanol, and the solvent was removed under vacuum. The polypropylene product (3.6 g) was collected by washing with acetone and drying under vacuum.

EXAMPLE 4

This Example illustrates the use of the product from Example 1 as a cocatalyst in the polymerization of propylene.

Six milligrams of Cp'.sub.2 ZrMe.sub.2 (Cp'=.eta..sup.5 -C.sub.5 Me.sub.5) and 36 mg of the white solid obtained from Example 1 (Al/Zr=10.5) were mixed in a quartz pressure tube. Then, 4 mL of dry toluene and 10 mL of liquid propylene were condensed into the above tube at -78.degree. C. The reaction mixture was stirred at 0.degree. C. for twenty-five minutes. The reaction was quenched with methanol. After removing the solvent, the polypropylene product (3.4 g) was collected by washing with acetone and drying under vacuum.

EXAMPLE 5

This Example illustrates a second route for the synthesis of phenoxyaluminoxanes.

A commercial sample of methylaluminoxane (MAO, 0.60 g) was dissolved in 50 mL of toluene in a 500 mL flask and was cooled to -55.degree. C. A solution of pentafluorophenol (1.85 g) in 20 mL of toluene was then added dropwise to the above solution. It was slowly warmed to room temperature and stirred for ten hours. A white solid in quantitative yield was collected after removing solvent under vacuum.

EXAMPLE 6

This Example illustrates the use of the product from Example 5 as a cocatalyst in the polymerization of propylene.

Six milligrams of Cp'.sub.2 ZrMe.sub.2 (Cp'=.eta..sup.5 -C.sub.5 Me.sub.5) and 40 mg of the white solid obtained from Example 5 (Al/Zr=12) were mixed in a 50 mL flask. Then 20 mL of propylene was condensed in at -78.degree. C. The reaction mixture was stirred at 0.degree. C. for three hours. The reaction was quenched with methanol. Solvent was then removed under vacuum. After washing and drying, 3.3 g of polypropylene was collected.

EXAMPLE 7

This Example illustrates the use of the product from Example 5 as a cocatalyst in the isotactic polymerization of propylene.

Six milligrams of Me.sub.2 Si(C.sub.5 Me.sub.4)(C.sub.5 H.sub.3 R*)ZrMe.sub.2 (R*=(+)-neomenthyl) and 31 mg of the white solid obtained from Example 5 (Al/Zr=12.5) were mixed in a 50 mL flask. Then 20 mL of dry propylene was condensed in at -78.degree. C. The reaction mixture was stirred at 0.degree. C. for three hours. A reaction was quenched with methanol. Solvent was then removed under vacuum. After washing and drying, 0.80 g of white solid polypropylene was collected, and .sup.13 C NMR (1,2,4-trichlorobenzene, 130.degree. C.) showed the "mmmmm" pentad in this

material at greater than 90%.

EXAMPLES 8-13

The Table set forth below gives the results of propylene polymerizations conducted at 30.degree. C. one atmosphere, in 250 ml of toluene using two differing zirconium-containing metallocenes with various aluminoxanes at a 250:1 molar ratio of Al:Zr. All values are given in terms of 10.sup.5 g polypropylene/mole Zr.hr.atm:

Metallocene	PMAO.sup.(1)	Me.sub.2 AlO.phi.F.sub.5 + H.sub.2 O.sup.(2)	Me.sub.2 AlO.phi.F.sub.5 + CuSO.sub.4.5H.sub.2 O.sup.(3)
Cp.sub.2 ZrMe.sub.2	0.40.sup.(4)	0.40	1.13.sup.(5)
Cp.sub.2 ZrCl.sub.2	1.35.sup.(6)	0.81	1.07

.sup.(1) PMAO = polymethylaluminoxane. Used as a control and not as part of the present invention.
.sup.(2) The molar ratio of water to aluminum was 0.4:1.
.sup.(3) The molar ratio of water to aluminum was 1:1.
.sup.(4) Average of six runs.
.sup.(5) Average of runs of 1.07 and 1.19.
.sup.(6) Average of five runs.

EXAMPLES 14-17

The following propylene polymerization data was generated analogous to that shown in Examples 8-13 using less aluminoxane and a higher zirconium content (a 25:1 ratio of Al:Zr):

Metallocene + H.sub.2 O.sup.(1)	Me.sub.2 AlO.phi.F.sub.5	Me.sub.2 AlO.phi.F.sub.5 + CuSO.sub.4.5H.sub.2 O.sup.(2)
Cp.sub.2 ZrMe.sub.2	0.13	0.28
Cp.sub.2 ZrCl.sub.2	0.15	0.22

.sup.(1) The molar ratio of water to aluminum was 0.4:1.

.sup.(2) The molar ratio of water to aluminum was 1:1.

EXAMPLES 18-20

The Table set forth below gives the results (10.sup.5 g polypropylene/mole Zr.hr.atm) of other polymerizations of propylene at 30.degree. C., one atmosphere, 250 ml toluene, and 250:1 ratio of Al:Zr:

Aluminoxane Used	Metallocene Used Cp.sub.2 ZrMe.sub.2	Cp.sub.2 ZrCl.sub.2
Et.sub.2 AlO.phi.F.sub.5 + H.sub.2 O (0.5:1).sup.(2)	0.80.sup.(1)	0.81
(iBu).sub.2 AlO.phi.F.sub.5 + H.sub.2 O (0.4:1).sup.(2)	0.60	

.sup.(1) Average of runs of 0.71 and 0.89.
.sup.(2) This indicates the molar ratio of water to aluminum.

EXAMPLES 21-23

Ethylene polymerizations were conducted at 80.degree. C., three atmospheres pressure, in 250 ml of toluene, with a 3.14.times.10.sup.5 molar ratio of Al:Zr using dicyclopentadienyl zirconium dichloride as the metallocene:

Aluminoxane Used	Productivity.sup.(1)
PMAO	2.35.sup.(2)
Me.sub.2 AlO.phi.F.sub.5 + H.sub.2 O (0.4:1)	1.11
(iBu).sub.2 AlO.phi.F.sub.5 + H.sub.2 O (0.4:1)	0.70

.sup.(1) Measured as 10.sup.6 gm. PE/ gm. Zr hr. atm.
.sup.(2) Average of eight runs.

EXAMPLE 24

This Example is similar to Examples 21-22 but utilizes a phenoxy group with electron

donating substituents on the phenyl ring. The product of the reaction of triisobutylaluminum and 2,6-di-t-butyl-paracresol (1:1 mole ratio), or 2,6-di-t-butyl-4-methyl-phenoxide, was converted to an aluminoxane with water (0.65:1 water to aluminum mole ratio). This aluminoxane was used in ethylene polymerization with zirconocene dichloride under the same reaction conditions used in Examples 21-22. The polyethylene produced amounted to 0.51.times.10.sup.6 g. PE/ g. Zr.hr.atm.

The foregoing Examples, since they are intended to merely set forth only certain embodiments of the present invention, should not be construed in a limiting sense. The scope of protection sought is set forth in the Claims which follow.

United States Patent **5,965,566**
Greenwald , et al. **October 12, 1999**

High molecular weight polymer-based prodrugs

Abstract

The present invention is directed compositions of the formula: ##STR1## wherein: D is a residue of biologically active moiety; X is an electron withdrawing group; Y and Y' are independently O or S; (n) is zero (0) or a positive integer, preferably from 1 to about 12; wherein: R.sub.1 and R.sub.2 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls; wherein: R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted allyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR2## wherein: R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring. In preferred embodiments, the prodrugs contain a polyethylene glycol having a molecular weight of at least about 20,000.

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Assignee: **Enzon, Inc.** (Piscataway, NJ)

Appl. No.: **914927**

Filed: **August 20, 1997**

Current U.S. Class: **514/279**; 514/283; 514/449; 546/48; 546/51; 549/510; 549/511

Intern'l Class: A61K 031/44; C07D 491/22

Field of Search: 514/279,283,449 546/48,51 549/510,511

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Primary Examiner: Trinh; Ba K.
Attorney, Agent or Firm: Roberts & Mercanti, L.L.P.

Parent Case Text

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08/700,269 filed Aug. 20, 1996, now U.S. Pat. No. 5,840,900 which, in turn, is a continuation-in-part of U.S. patent application Ser. No. 08/537,207 filed Sep. 29, 1995, now U.S. Pat. No. 5,880,131, which, in turn, is a continuation-in-part of U.S. patent application Ser. No. 08/380,873 filed Jan. 30, 1995, now U.S. Pat. No. 5,614,549 which, in turn, is a continuation-in-part of U.S. patent application Ser. No. 08/140,346 filed Oct. 20, 1993 now abandoned. The contents of each of the foregoing applications are incorporated herein by reference.

Claims

We claim:

1. A composition comprising the formula: ##STR18## wherein: D is a residue of biologically active moiety;

X is an ***electron withdrawing group***;

Y and Y' are independently O or S;

(n) is zero (0) or a positive integer;

R.sub.1 and R.sub.2 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6, alkyls;

R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted alkyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR19## R.sub.4

and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring.

2. The composition of claim 1, wherein R.sub.3 is a substantially non-antigenic polymer having a capping group Z.

3. The composition of claim 2, wherein Z is selected from the group consisting of OH, C.sub.1-4 alkyl moieties, or ##STR20## wherein D' is selected from the group consisting of D, biologically active moieties other than D, dialkyl ureas, C.sub.1-4 alkyls and carboxylic acids.

4. The composition of claim 1, wherein R.sub.1 and R.sub.2 are independently H, methyl or ethyl.

5. The composition of claim 1, wherein said substituted C.sub.1-6 alkyl is selected from the group consisting of carboxyalkyls, aminoalkyls, dialkylaminos, hydroxyalkyls, and mercaptoalkyls.

6. The composition of claim 1, wherein X is selected from the group consisting of O, N(R.sub.1), S, SO and SO.sub.2.

7. The composition of claim 1, wherein X is selected from the group consisting of O and N(R.sub.1).

8. The composition of claim 1, wherein (n) is zero (0), 1, or 2.

9. The composition of claim 1, wherein Y and Y' are O.

10. The composition of claim 1, wherein R.sub.3 comprises a polyalkylene oxide.

11. The composition of claim 10, wherein said polyalkylene oxide comprises polyethylene glycol.

12. The composition of claim 10, wherein said polyalkylene oxide has a molecular weight of from about 20,000 to about 80,000.

13. The composition of claim 10, wherein said polyalkylene oxide has a molecular weight of from about 25,000 to about 45,000.

14. The composition of claim 13, wherein said polyalkylene oxide has a molecular weight of from about 30,000 to about 42,000.

15. The composition of claim 11, wherein R.sub.3 is selected from the group consisting of:

--C(Y)--(CH.sub.2).sub.n --(CH.sub.2 CH.sub.2 O).sub.x --R"; --C(Y)--Y--(CH.sub.2).sub.n --(CH.sub.2 CH.sub.2 O).sub.x --R";

--C(Y)--NR.sub.1 --(CH.sub.2).sub.n --(CH.sub.2 CH.sub.2 O).sub.x --R"; and --CHR.sub.1 --(CH.sub.2).sub.n --(CH.sub.2 CH.sub.2 O).sub.x --R";

wherein

R.sub.1 is independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls;

(n) is zero (0) or is a positive integer;

Y is O or S;

R" is a capping group or R.sub.1 ; and

(x) represents the degree of polymerization.

16. A composition of claim 1 having the formula: ##STR21## wherein R.sub.1 is H or CH.sub.3 ; and X is O or S.

17. The composition of claim 1, wherein D is selected from the group consisting of paclitaxel, taxotere, camptothecin and podophyllotoxin.

18. The composition of claim 1, wherein D is a member of the group consisting of paclitaxel and taxotere and Y' is attached to the 2' position of said paclitaxel, taxane or taxotere residues.

19. The composition of claim 17, wherein D is a camptothecin derivative residue and Y' is attached to the 20S position of said camptothecin derivative.

20. The composition of claim 1, wherein D is a residue selected from the group consisting of biologically active proteins, enzymes, peptides, anti-tumor agents, cardiovascular agents, anti-neoplastics, anti-infectives, anti-fungals, anti-anxiety agents, gastrointestinal agents, central nervous system-activating agents, analgesics, fertility agents, contraceptive agents, anti-inflammatory agents, steroidal agents, anti-urecemic agents, vasodilating agents, and vasoconstricting agents.

21. A method of treating mammals with prodrugs, comprising:

administering to a mammal in need of such treatment an effective amount of a composition of claim 1.

22. A method of preparing a polymer-based prodrug having a circulation half-life greater

than its in-vivo hydrolysis half-life, comprising:

reacting a biologically active moiety containing an available hydroxyl group with a bifunctional spacer moiety containing an available carboxylic acid group in the presence of a first coupling agent to form a biologically active moiety--spacer prodrug intermediate,

reacting said biologically active moiety--spacer prodrug intermediate with a substantially non-antigenic polymer containing a terminal group selected from the group consisting of carboxylic acid, amine and hydroxyl in the presence of a second coupling agent and recovering the polymer-based prodrug.

23. The method of claim 22, wherein said biologically active moiety is selected from the group consisting of biologically active proteins, enzymes, peptides, anti-tumor agents, cardiovascular agents, anti-neoplastics, anti-infectives, anti-fungals, anti-anxiety agents, gastrointestinal agents, central nervous system-activating agents, analgesics, fertility agents, contraceptive agents, anti-inflammatory agents, steroidal agents, anti-urecemic agents, vasodilating agents, and vasoconstricting agents.

24. The method of claim 22, wherein said bifunctional spacer moiety is selected from the group consisting of diglycolic acid, thiodiglycolic acid, l-alanine, d-alanine, hydroxyacetic acid and bromoacetic acid.

25. The method of claim 22, wherein said first and said second coupling agents are independently selected from the group consisting of 1,3-diisopropylcarbodiimide (DIPC), dialkyl carbodiimides, 2-halo-1-alkyl-pyridinium halides, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC), propane phosphonic acid cyclic anhydride (PPACA) and carbodiimide (CDI).

26. The method of claim 22, wherein said substantially non-antigenic polymer containing a terminal carboxylic acid group or a terminal amine group comprises a polyalkylene oxide.

27. The method of claim 26, wherein said polyalkylene oxide has a molecular weight of from about 20,000 to about 80,000.

28. A method of preparing a biologically active nucleophile conjugate, comprising:

contacting a biologically active nucleophile with a compound of the formula: ##STR22## wherein: X is an ***electron withdrawing group***;

Y and Y' are independently O or S;

(n) is zero (0) or a positive integer;

R.sub.1 and R.sub.2 are independently selected from the group consisting of H, C.sub.1-6

alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls;

R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted alkyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR23## R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring;

Z.sup.1 and Z.sup.2 are independently CO.sub.2 H, CO.sub.2 R.sub.6, OR.sub.7, CONR.sub.1 R.sub.8, H, a C.sub.1-4 alkyl ##STR24## where R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring;

R.sub.6 is R.sub.4 or an N-hydroxysuccinimide, an N-hydroxybenzotriazole, an N-acyl thazolidine, imidazole or an acid activating group;

R.sub.7 is R.sub.4 or C(O)-halogen, para nitrophenyl carbonate, imidazolyl carbonate, or N-hydroxysuccinimidyl carbonate; and

R.sub.8 is R.sub.4 or CR.sub.1 R.sub.2 CO.sub.2 H;

and recovering the resultant biologically active nucleophile conjugate.

29. A method of forming a camptothecin-based conjugate, comprising:

1) forming a camptothecin derivative containing bifunctional spacer containing moiety, by contacting said camptothecin derivative with a bifunctional spacer containing moiety in the presence of a coupling agent;

2) forming the trihaloacetic acid deriviative of said camptothecin derivative containing said bifunctional spacer containing moiety; and

3) reacting said trihaloacetic acid derivative of said camptothecin derivative containing said bifunctional spacer containing moiety with a diacid derivative of a substantially non-antigenic polymer.

30. A compound comprising the formula: ##STR25## wherein: D is a residue of biologically active moiety;

X is an ***electron withdrawing group***;

Y and Y' are independently O or S;

(n) is zero (0) or a positive integer;

R.sub.1 and R.sub.2 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls;

R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted alkyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR26## R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring.

31. The compound of claim 30, wherein R.sub.1 and R.sub.2 are H.

32. The compound of claim 30, wherein R.sub.3 comprises a polyalkylene oxide.

33. The compound of claim 32, wherein said polyalkylene oxide comprises polyethylene glycol.

34. The compound of claim 32, wherein said polyalkylene oxide has a molecular weight of from about 20,000 to about 80,000.

35. The compound of claim 30 having the formula: ##STR27## wherein all variables are as set forth above.

36. The compound of formula 30, wherein D is a residue of an anti-fungal agent.

37. The compound of formula 35, wherein D is a residue of an anti-fungal agent.

38. A method of preparing prodrugs, comprising:

reacting an amino acid ester of a hydroxy-containing biologically-active moiety with a carboxylic acid of a substantially non-antigenic polymer derivative or a carboxylic acid derivative of a substantially non-antigenic polymer in the presence of a coupling agent.

39. The method of claim 38, wherein said amino acid ester of a hydroxy-containing biologically-active moiety is a 20-O-amino acid ester of a camptothecin derivative.

40. The method of claim 39, wherein said 20-O-amino acid ester of camptothecin is selected form the group consisting of camptothecin-20-O-(l)-alanate, camptothecin-20-O-(d)-alanate and racemic mixtures thereof.

41. The method of claim 38, wherein said coupling agent is 1,3-diisopropylcarbodiimide (DIPC).

42. The method of claim 38, wherein said hydroxy-containing biologically-active moiety is a hydroxyl-containing anti-fungal agent.

43. A compound comprising the formula: ##STR28## D is a residue of biologically active moiety; X is an electron withdrawing group;

Y and Y' are independently O or S;

(n) is zero (0) or a positive integer;

R.sub.1 and R.sub.2 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls;

R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted alkyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR29## R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring.

44. The compound of claim 43, wherein R.sub.1 and R.sub.2 are H and X is O.

45. The compound of claim 44, wherein R.sub.3 comprises a polyalkylene oxide.

46. The compound of claim 45, wherein said polyalkylene oxide comprises polyethylene glycol.

47. The compound of claim 46, wherein said polyalkylene oxide has a molecular weight of from about 20,000 to about 80,000.

48. The compound of claim 43, wherein D is a residue of a hydroxyl-containing anti-fungal agent.

49. A compound comprising the formula: ##STR30## wherein: D is a residue of biologically active moiety;

X is an electron with drawing group;

Y and Y' are independently O or S;

(n) is zero or a positive integer;

R.sub.1 and R.sub.2 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls;

R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted alkyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR31## R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring.

50. The compound of claim 49, wherein D is a residue of a hydroxyl-containing anti-fungal agent and X is NH.

51. A compound comprising the formula: ##STR32## wherein: D is a residue of biologically active moiety;

X is an electron with drawing group;

Y and Y' are independently O or S;

(n) is zero or a positive integer;

R.sub.1 and R.sub.2 are selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C.sub.1-6 alkyls;

R.sub.3 is a substantially non-antigenic polymer, C.sub.1-12 straight or branched alkyl or substituted alkyl, C.sub.5-8 cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or ##STR33## R.sub.4 and R.sub.5 are independently selected from the group consisting of H, C.sub.1-6 alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C.sub.1-6 alkyls or jointly form a cyclic C.sub.5 -C.sub.7 ring.

52. The compound of claim 51, wherein D is a residue of a hydroxyl-containing anti-fungal agent and X is NH.

Description

TECHNICAL FIELD

The present invention relates to water soluble prodrugs. In particular, the invention relates to the use of relatively high molecular weight non-antigenic polymers to prepare prodrugs.

BACKGROUND OF THE INVENTION

United States Patent **5,985,895**
Wermuth , et al. **November 16, 1999**

2-naphthamide derivatives and their therapeutic applications

Abstract

The invention relates to 2-naphthamide derivatives, in the form of bases or of salts, corresponding to the following general formula (I): ##STR1## in which: the Z-Y entity represents an N--CH.sub.2, C.dbd.CH or CH--CH.sub.2 group; R.sup.1 represents a hydrogen, fluorine, bromine or iodine atom or a hydroxyl, methoxy, nitrile or nitro group; R.sup.2 represents a hydrogen or bromine atom or a hydroxyl, methoxy, nitrile or nitro group; the R.sub.1 and R.sub.2 substituents both being situated on the same ring of the naphthamide unit or each being situated on one of the rings; R.sup.3 and R.sup.4 can be identical or different and each independently represent a hydrogen or chlorine atom or a methoxy or methyl group or an electron-withdrawing group. The invention also relates to their therapeutic applications as partial agonists of the dopamine D.sub.3 receptor. The invention applies more particularly to the treatment of neuropsychiatric conditions involving the dopamine D.sub.3 receptor, in particular psychotic and depressive states, to the treatment of drug-dependence states or to the treatment of disorders of a sexual nature.

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Parent Case Text

PRIOR APPLICATION

This application is a division of U.S. patent application Ser. No. 762,782, filed Dec. 10, 1996, now U.S. Pat. No. 5,872,119.

Claims

We claim:

1. A 2-Naphthamide in the form of bases or of salts of a compound of the formula ##STR6## in which: Z--Y is C.dbd.CH or CH--CH.sub.2

R.sup.1 is selected from the group consisting of hydrogen, fluorine, bromine, iodine, hydroxyl, methoxy, nitrile and nitro;

R.sup.2 is selected from the group consisting of hydrogen, bromine, hydroxyl, methoxy,

nitrile and nitro;

the R.sub.1 and R.sub.2 substituents both being situated on the same ring of the naphthamide unit or each being situated on one of the rings;

R.sup.3 and R.sup.4 are individually selected from the group consisting of hydrogen, chlorine, methoxy, methyl and an ***electron-withdrawing group***.

2. A compound of claim 1 selected from the group consisting of N-[4-(4-phenyl-1,2,3,6-tetrahydropyridinyl)-butyl]-2-naphthamide and N-[4-(4-phenylpiperidinyl)-butyl]-2-naphthamide.

3. A compound of claim 1 wherein R.sub.1 and R.sub.2 are hydrogen.

4. A compound of claim 1 wherein R.sub.1 is in the 1-position and is other than methoxy and R.sub.2 is on the second ring of the naphthamide group.

5. A therapeutic composition comprising a partial agonistically effective amount of a dopamine D.sub.3 receptor of a compound of claim 1 and an inert pharmaceutical carrier.

6. A therapeutic composition comprising a partial agonistically effective amount of a dopamine D.sub.3 receptor of a compound of claim 2 and an inert pharmaceutical carrier.

7. A method of treating a human suffering from Parkinson's disease comprising administering to said human a partial agonistically effective amount of dopamine D.sub.3 receptor of claim 2.

8. A compound of claim 1 with no substituent in the 1,3- and 4-positions of the naphthamide.

9. A method of inducing a partial agonist activity of dopamine D.sub.3 receptor in warm-blooded animals comprising administering to warm-blooded animals an amount of a compound of claim 1 sufficient to induce a partial antagonistically effective activity of dopamine D.sub.3 receptors.

10. The method of claim 7 wherein the warm-blooded animal is a human suffering from Parkinson's disease and receiving treatment therefor.

11. The method of claim 9, wherein the administered compound is selected from the group consisting of N-[4-(4-phenyl-1,2,3,6-tetrahydropyridinyl)-butyl]-2-naphthamide and N-[4-(4-phenylpiperidinyl)-butyl]-2-naphthamide.

12. The method of claim 9, wherein R.sub.1 is in the 1-position and is other than methoxy and R.sub.2 is on the second ring of the naphthamide group.

13. The method of claim 9 with no substituent in the 1,3- and 4-positions of the

naphthamide group.

14. The method of claim 9 wherein R.sub.1 and R.sub.2 are hydrogen.

Description

The present invention relates to new chemical compounds derived from 2-naphthamides and to their therapeutic applications, in particular as selective dopaminergic agents.

Many phenylpiperazine derivatives are known and used for their activity with respect to the central nervous system, in particular for their neuroleptic properties.

Phenylpiperazines are known essentially as serotoninergic agents.

As regards the dopamine receptors, it has been shown that some arylpiperazine derivatives exhibit a higher affinity for the dopamine D.sub.3 receptor, in comparison with other dopamine receptors (Murray P. J. et al., Bioorganic & Medicinal Chemistry Letters, vol. 5, No. 3, pp 219-222 (1995)).

According to this document, these compounds, which exhibit a degree of selectivity with respect to the dopamine D.sub.3 receptor in comparison with other receptors, could be used to verify the hypothesis that a selective antagonist of the dopamine D.sub.3 receptor could furnish an effective antipsychotic agent which does not have extra-pyramidal side effects.

Moreover, it has been shown that some naphthamide derivatives behaved as pure antagonists of the D.sub.3 receptor and could therefore be used for the preparation of medicaments which are antagonists of dopamine by blockage of the D.sub.3 receptor (French Patent Application No. 91 13103).

Recently, naphthamide derivatives of arylpiperazines have also been described, in Patent U.S. Pat. No. 5,395,835, as selective antagonists of the dopamine D.sub.3 receptor. These compounds are useful as antipsychotic agents and for the treatment of disorders related to dopaminergic blockage.

It is in this state of knowledge that the Inventors have demonstrated, in an entirely surprising and unexpected way, that 2-naphthamide derivatives of formula (I) given below exhibited a strong affinity for dopaminergic receptors and in particular for the D.sub.3 receptor and that they behaved selectively as powerful partial agonists of dopamine at the D.sub.3 receptor.

Thus, the subject of the present invention is 2-naphthamide derivatives, in the form of bases or of salts, corresponding to the general formula (I): ##STR2## in which: the Z-Y entity represents an N--CH.sub.2, C.dbd.CH or CH--CH.sub.2 group;

R.sup.1 represents a hydrogen, fluorine, bromine or iodine atom or a hydroxyl, methoxy, nitrile or nitro group;

R.sup.2 represents a hydrogen or bromine atom or a hydroxyl, methoxy, nitrile or nitro group;

the R.sub.1 and R.sub.2 substituents both being situated on the same ring of the naphthamide unit or each being situated on one of the rings;

R.sup.3 and R.sup.4 can be identical or different and each independently represent a hydrogen or chlorine atom or a methoxy or methyl group or an electron-withdrawing group.

A further subject of the invention is pharmaceutical compositions comprising a therapeutically effective amount of at least one derivative of abovementioned formula (I), in the base form or in the form of a pharmaceutically acceptable salt, in combination with a pharmaceutically acceptable vehicle or excipient.

It further relates to medicaments acting as partial agonists of the dopamine D.sub.3 receptor comprising, as active principle, at least one derivative of abovementioned formula (I) and to the use of the said derivatives for the preparation of such medicaments.

The derivatives according to the invention are represented by the general formula (I). These compounds are novel.

Naphthamide derivatives of arylpiperazines may be found in the literature (abovementioned U.S. Pat. No. 5,395,835) but, in these compounds, the piperazine unit is separated from the naphthamide unit by a chain containing 2 carbon atoms whereas, according to the invention, the chain exhibits 4 carbon atoms.

The derivatives according to the invention can be provided in the form of free bases or in the form of salts, in particular in the form of addition salts with physiologically acceptable acids, and the invention also applies to these various forms.

According to the invention, the derivatives for which the Z-Y entity represents an N--CH.sub.2 group constitute preferred derivatives.

Mention may be made, as particularly preferred derivatives according to the invention, of the following compounds:

N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-1-methoxy-4-nitro-2-naphthamide ;

N-[4-(4-phenyl-1,2,3,6-tetrahydropyridinyl)butyl]-2-naphthamide;

N-[4-(4-phenylpiperidinyl)butyl]-2-naphthamide;

N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-1-methoxy-4-cyano-2-naphthamide ;

N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-2-naphthamide;

N-[4-(4-(2-chlorophenyl)piperazinyl)butyl]-3-methoxy-2-naphthamide;

N-[4-(4-(2-chlorophenyl)piperazinyl)butyl]-2-naphthamide;

N-[4-(4-(3-chlorophenyl)piperazinyl)butyl]-2-naphthamide;

N-[4-(4-phenylpiperazinyl)butyl]-2-naphthamide;

N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-1-methoxy-2-naphthamide oxalate.

The derivatives of formula (I) according to the present invention can be prepared by known methods (W. Adcock et al., Aust. J. Chem., 1965, 18, 1351).

The suitably substituted acid part (2-naphthoic acid) is converted to the mixed anhydride with isobutyl chloroformate in acetone or any other solvent, in basic medium, and reacted with the desired amine as shown in the following reaction scheme: ##STR3##

Other methods for activating the carboxyl functional group can also be used; in fact, any method for the preparation of an amide is suitable, including the use of the corresponding acid chlorides.

Aminopiperazines of type B are obtained by conventional methods, often starting from commercially available phenylpiperazines, by alkylation by means of chlorobutyronitrile in basic medium in an alcoholic solvent. The nitrile functional group is then reduced to a primary amine, either with LiAlH.sub.4 or by catalytic hydrogenation in the presence of palladium (Pd)-on-charcoal. ##STR4##

Aminobutylphenyltetrahydropyridines of type C or aminobutylphenylpiperidines of type D are also obtained by conventional methods, either from commercially available products or from N-Boc-4-piperidone (where Boc means tert-butoxycarbonyl), which is reacted with a phenylmagnesium derivative and which is then dehydrated in order to obtain the corresponding tetrahydropyridine. The corresponding piperidine is obtained by catalytic hydrogenation of the latter. The t-butoxycarbonyl (Boc) protection is hydrolysed in acid medium and the nitrogen is alkylated with bromobutyronitrile in basic medium in the same way as above. The scheme for the preparation of the compounds C and D is given below: ##STR5##

The invention will be described in more detail below using the following examples given by way of illustration and without limitation.

EXAMPLES

Example 1

Preparation of N-[4-(4-(2-methoxyphenyl)-piperazinyl)butyl]-1-methoxy-4-nitro-2-naphthami de (Do 885)

120 mg of 1-methoxy-4-nitronaphthalene-2-carboxylic acid A (prepared as indicated below in a)) are dissolved in 15 ml of anhydrous acetone in a 25 ml two-necked flask. 2.5 equivalents of triethylamine are added and the mixture is cooled to -15.degree. C. by means of a dry ice/acetone bath. 1.05 equivalents of isobutyl chloroformate are then added to the mixture, which is allowed to react for 1 hour at -15.degree. C. 1.05 equivalents of N-(4-aminobutyl)-N'-(2-methoxyphenyl)piperazine B (prepared as indicated below in b)) are then added and reaction is allowed to take place for 2 hours at room temperature under an inert atmosphere. The triethylamine hydrochloride is filtered off and the filtrate is evaporated to dryness. The residue is taken up in a small amount of ethyl acetate and the naphthamide is purified by chromatography on a silica column (eluent: AcOEt/MeOH 90/10). The naphthamide is crystallized from diethyl ether. 85 mg of yellow crystals are obtained. Y=37%. M.p.=109.degree. C. .sup.1 H NMR (CDCl.sub.3): 1.59-1.73 (m, 2H, --CH.sub.2 --), 2.47-2.66 (m, 6H, --H.sub.2 C--CH.sub.2 --CH.sub.2 --), 3.02-3.20 (m, 4H, --CH.sub.2 --CH.sub.2 --), 3.58-3.61 (m, 4H, --H.sub.2 C--CH.sub.2 --), 3.86 (s, 3H, OCH.sub.3, phenyl), 4.08 (s, 3H, OCH.sub.3, naphthyl), 6.79-7.03 (m, 4H, --HC--CH--CH--CH--, phenyl), 7.68-7.85 (m, 2H, --HC--CH--), 8.27-8.31 (d, 1H, --CH--), 8.62-8.66 (d, 1H, --CH--), 8.87 (s, 1H, --CH--).

Analysis C.sub.27 H.sub.32 N.sub.4 O.sub.5 ; Cal. % C 65.84, % H 6.55, % N 11.37; Fd. % C 66.25, % H 6.43, % N 11.12

a) Preparation of 1-methoxy-4-nitro-2-naphthoic acid (A)

Methyl ester of 1-methoxy-2-naphthoic acid

1.88 g (10 mmol) of 1-hydroxy-2-naphthoic acid are suspended in 50 ml of methyl ethyl ketone. 2.76 g (2 equivalents) of anhydrous potassium carbonate are added and then 2.51 g (2 equivalents) of dimethyl sulphate, in solution in the solvent, are added dropwise. The mixture is heated at reflux with stirring overnight, then, after cooling, the excess potassium carbonate is filtered off and the filtrate is concentrated. The evaporation residue is taken up in water and extracted a number of times with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and then evaporated. Purification is carried out by chromatography on a silica column (eluent: hexane/ethyl acetate 90/10). A golden oil is obtained. Y=82%. .sup.1 H NMR (CDCl.sub.3): 4.00 (3H, s, CO.sub.2 CH.sub.3), 4.08 (3H, s, OCH.sub.3, 7.55-7.63 (3H, m, HC--CH--CH), 7.83-7.90 (2H, m, HC--CH), 8.27-8:32 (1H, m, CH). .sup.13 C NMR (CDCl.sub.3): 52.1 (OCH.sub.3), 58.3 (OCH.sub.3), 166.4 (C.dbd.O), 158.1 (C--O, .alpha.), 119.0 (C--C.dbd.O, .beta.), 126.3 (C--H, .beta.), 123.4 (C--H, .alpha.), 128.2 (C--H, .alpha.), 128.4 (C--H, .beta.), 127.7 (C--H, .beta.), 127.6 (C--H, .alpha.), 128.6 (C--C, .gamma.), 136.6 (C--C, .gamma.)

Methyl ester of 1-methoxy-4-nitro-2-naphthoic acid

2 g of methyl ester of 1-methoxy-2-naphthoic acid are dissolved in 15 ml of glacial acetic acid. 1.2 equivalents of concentrated nitric acid, in solution in glacial acetic acid, are added dropwise and reaction is allowed to take place for 4 hours at room temperature with good stirring. The reaction mixture is slowly hydrolysed in ice. The methyl ester of 1-methoxy-4-nitro-2-napthoic acid precipitates. The precipitate is filtered off, washed a number of times with ice-cold water, then redissolved in ethyl acetate, washed with water and then with a saturated potassium carbonate solution (note 1), in order to remove the residual acetic acid, and finally washed with water. The mixture is dried over sodium sulphate and concentrated. Purification is carried out by chromatography on a silica column (eluent: hexane/CH.sub.2 Cl.sub.2 60/40). Yellow crystals: Y=89%. Melting p.: 110.degree. C. .sup.1 H NMR (CDCl.sub.3): 4.02 (3H, s, --CO.sub.2 CH.sub.3), 4.14 (3H, s, --OCH.sub.3), 7.65-7.86 (2H, m, --HC--CH), 8.39-8.43 (1H, dd, --CH), 8.62-8.66 (1H, dd, --CH), 8.74 (1H, s, --CH). .sup.13 C NMR (CDCl.sub.3): 52.7 (--OCH.sub.3), 64.0 (--OCH.sub.3), 164.5 (>C.dbd.O), 162.9 (>C--O, .alpha.), 116.9 (>C--C.dbd.O, .beta.), 124.4 (>C--H, .beta.), 129.5 (>C--NO.sub.2, .alpha.), 141.5 (>C--C, .gamma.), 123.6 (>C--H, .alpha.), 131.8 (>C--H, .beta.), 127.9 (>C--H, .beta.), 126.6 (>C--H, .alpha.), 128.2 (>C--C, .gamma.).

Note 1: It is preferable not to use sodium hydroxide because it forms a highly coloured complex which is difficult to remove. It is important to thoroughly wash the precipitate beforehand in order to remove as much as possible of the acid as the neutralization of acetic acid by K.sub.2 CO.sub.3 gives off carbon dioxide.

1-Methoxy-4-nitro-2-naphthoic acid (A)

750 mg of methyl ester of 1-methoxy-4-nitro-2-naphthoic acid are dissolved in 20 ml of methanol. 1.5 equivalents of sodium hydrogencarbonate are added and the mixture is heated at reflux for 10 hours. The mixture is concentrated and the residue is taken up in water. Extraction is carried out with ether in order to remove the organic impurities and the aqueous phase is acidified to pH=2 with 5N hydrochloric acid. A yellowish-white precipitate is obtained. Extraction is carried out with ethyl acetate, washing with water is carried out 3 times, drying is carried out over sodium sulphate and the mixture is concentrated. The acid is crystallized from pentane. Purification is carried out by hot recrystallization from water and addition of active charcoal in order to remove the impurities. Yellowish-white crystals. Y=94%.

b) Preparation of N-(4-aminobutyl)-N'-(2-methoxyphenyl)piperazine (B)

N-(2-methoxyphenyl)-N'-(3-cyanopropyl) piperazine

8 g of N-(2-methoxyphenyl)piperazine are suspended in 150 ml of acetonitrile. 2.5 equivalents of anhydrous potassium carbonate are added and then 1.05 equivalents of 4-bromobutyronitrile, in solution in acetonitrile, are added dropwise. The mixture is heated

at reflux for 10 hours and then filtered and the filtrate is concentrated. The residue is taken up in ethyl acetate and washed 3 times with water. The organic phase is extracted with a 1M hydrochloric acid solution and the acid phase is washed with ethyl acetate. The acid phase is neutralized with 28% aqueous ammonia to pH>11. Extraction is carried out with ethyl acetate, the organic phase is washed with water and dried over anhydrous sodium sulphate and the mixture is concentrated. The nitrile is crystallized from hexane and recrystallized while hot from the same solvent. 6.8 g of nitrile are obtained. Y=75%.

M.p.=74.degree. C. .sup.1 H NMR (CDCl.sub.3): 1.80-1.94 (m, 2H, --CH.sub.2 --), 2.43-2.57 (m, 4H, --CH.sub.2 --CH.sub.2 --), 2.62-2.67 (broad t, 4H, --CH.sub.2 --N<), 3.09 (broad s, 4H, >N--CH.sub.2 --), 3.87 (s, 3H, --OCH.sub.3), 6.85-7.04 (m, 4H, --CH--CH--CH--CH--). .sup.13 C NMR (CDCl.sub.3): 14.9 (--CH.sub.2 --CH.sub.2 --C.tbd.N), 22.7 (--CH.sub.2 --C.tbd.N), 50.5 (--CH.sub.2 --N--(CH.sub.2).sub.2 --), 53.2 (>C--N--(CH.sub.2).sub.2 --), 55.3 (--OCH.sub.3), 56.3 (>N--CH.sub.2 --), 111.1 (--CH--C--OCH.sub.3), 118.1 (--CH--CH--C--OCH.sub.3), 119.8 (--C.tbd.N) 120.9 (--CH--C--N<), 122.9 (--CH--CH--C--N<), 141.1 (>C--N<), 152.2 (--C--OCH.sub.3).

N-(4 -Aminobutyl)-N'-(2 -methoxyphenyl)piperazine (B)

1.2 g of lithium aluminium hydride are suspended in small portions (exothermic dissolution) in 50 ml of anhydrous diethyl ether (freshly distilled over sodium). 5 g of N-(2-methoxyphenyl)-N'-(3-cyanopropyl)piperazine, in solution in anhydrous tetrahydrofuran (THF), are added dropwise and heating is then carried out at reflux for 2 hours. The mixture is hydrolysed with a mixture of 5 ml of water in 25 ml of THF and allowed to stand overnight in order to enable the precipitate to agglomerate. The precipitate is filtered on celite, the filtrate is dried over anhydrous sodium sulphate and the filtrate is concentrated. Y=81%. .sup.13 C NMR (CDCl.sub.3): 24.3 (--CH.sub.2 --CH.sub.2 --CH.sub.2 --NH.sub.2), 31.9 (--CH.sub.2 --CH.sub.2 --NH.sub.2), 42.2 (--CH.sub.2 --NH.sub.2), 50.6 (--CH.sub.2 --N--(CH.sub.2).sub.2 --), 53.4 (>C--N--(CH.sub.2).sub.2 --), 55.3 (--OCH.sub.3), 58.6 (>N--CH.sub.2 --), 111.1 (--CH--C--OCH.sub.3), 118.1 (--CH--CH--COCH.sub.3), 120.9 (--CH--C--N<), 122.8 (--CH--CH--C--N<), 141.3 (>C--N<), 152.2 (--C--OCH.sub.3).

Example 2

Preparation of N-[4-(4-phenyl-1,2,3,6-tetrahydropyridinyl)butyl]-2-naphthamide (Do 911)

250 mg of naphthalene-2-carboxylic acid A (2-naphthoic acid) are suspended in 20 ml of anhydrous dichloromethane (freshly distilled over CaH.sub.2). 1.2 equivalents of oxalyl chloride are added at 0.degree. C. and then 2 drops of anhydrous dimethylformamide are added (to catalyse the chlorination reaction) and reaction is then allowed to take place at room temperature for 1 hour under an inert atmosphere (argon) and with vigorous stirring. The mixture is concentrated in order to remove the solvent and the excess oxalyl chloride and then the acid chloride formed is redissolved in 20 ml of dichloromethane. 1.05 equivalents of N-(4-aminobutyl)-4-phenyl-1,2,3,6-tetrahydropyridine C (prepared as

indicated below in c)) are added and reaction is allowed to take place for 2 hours at room temperature under an inert atmosphere (argon). The mixture is concentrated and the residue is taken up in a 3M aqueous hydrochloric acid solution. The acid phase is washed with ethyl acetate and then the aqueous phase is neutralized with a 32% aqueous ammonia solution to pH>11. Extraction is carried out with ethyl acetate, the organic phase is washed a number of times with water and dried over sodium sulphate and the mixture is concentrated. The residue is crystallized from a 50/50 ether/hexane mixture. 280 mg of white crystals are obtained. Y=50%. M.p.=172.degree. C. .sup.1 H NMR (CDCl.sub.3): 1.73-1.83 (m, 4H, --H.sub.2 C--CH.sub.2 --), 2.51-2.58 (t, 4H, --H.sub.2 C--CH.sub.2 --), 2.69-2.75 (t, 2H, --CH.sub.2 --), 3.11-3.16 (q, 2H, --CH.sub.2 --), 3.52-3.58 (2H, q, --CH.sub.2 --), 6.01-6.04 (1H, t, --CH.dbd.), 7.24-7.35 (5H, m, --(CH).sub.5 <, phenyl), 7.39-7.55 (m, 2H, >HC--CH<, naphthyl), 7.78-7.85 (4H, m, >HC--CH--CH--CH--CH<, naphthyl), 8.24 (1H, s, >CH--, naphthyl).

c) Preparation of N-(4-aminobutyl)-4-phenyl-1,2,3,6-tetrahydropyridine (C)

4-(4-Phenyl-1,2,3,6-tetrahydropyridinyl)-butyronitrile

5 g of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (very toxic compound: New Engl. J. Med., 1983, 309, 310; Science, 1983, 219, 979; Psychiatry Res., 1979, 1, 249) and then 100 ml of acetonitrile are introduced into a 250 ml round-bottomed flask. 2.5 equivalents of anhydrous potassium carbonate are added and then 1.05 equivalents of 4-bromobutyronitrile, in solution in acetonitrile, are added dropwise. The mixture is heated at reflux for 16 hours and then filtered, the precipitate is washed with acetone and the filtrate is concentrated. The residue is taken up in ethyl acetate and washed 3 times with water. The organic phase is extracted with a 3M hydrochloric acid solution and the acid phase is washed with ethyl acetate. The acid phase is neutralized with 28% aqueous ammonia to pH>11. Extraction is carried out with ethyl acetate, the organic phase is washed with water and dried over anhydrous sodium sulphate and the mixture is concentrated. The nitrile is purified by chromatography on a silica column (eluent: ethyl acetate/hexane 80/20). White crystals are obtained. M.p.=57-59.degree. C. Y=79%. .sup.1 H NMR (CDCl.sub.3, 330K): 1.81-1.95 (m, 2H, --CH.sub.2 --, 2.40-2.48 (t, 2H, --CH.sub.2 --), 2.54-2.60 (t, 4H, --H.sub.2 C--CH.sub.2 --), 2.67-2.72 (t, 2H, --CH.sub.2 --), 3.12-3.17 (q, 2H, --CH.sub.2 --), 6.06-6.09 (m, 1H, --CH.dbd.), 7.24-7.44 (m, 5H, phe). .sup.13 C NMR (CDCl.sub.3): 14.7 (--CH.sub.2 --CH.sub.2 --C.tbd.N), 22.8 (--CH.sub.2 --C.tbd.N), 27.7 (>C--CH.sub.2 --CH.sub.2 --N<, pyrid), 50.0 (--CH.sub.2 --CH.sub.2 --N<, pyrid), 52.9 (.dbd.CH--CH.sub.2 --N<, pyrid), 55.9 (>N--CH.sub.2 --), 119.6 (--CN), 121.3 (>CH--), 124.6 (.dbd.CH--, pyri), 126.8 (>(CH).sub.2 --), 128.1 (>CH).sub.2 --), 134.7 (>C.dbd.C--, pyri), 140.4 (>C<).

N-(4-Aminobutyl)-4-phenyl-1,2,3,6- tetrahydropyridine (C)

1.8 g of lithium aluminium hydride are suspended in small portions (exothermic dissolution) in 50 ml of anhydrous THF (freshly distilled over sodium). 4.5 g of 4-(4-phenyl-1,2,3,6-tetrahydropyridinyl)butyronitrile, in solution in THF, are added dropwise at 0.degree. C. and then reaction is allowed to take place at 0 C. for 3 hours with good

stirring. The mixture is hydrolysed with a mixture of 5 ml of water in solution in 50 ml of THF and the combined mixture is allowed to stand overnight in order to agglomerate the precipitate. The precipitate is filtered on celite and the filtrate is dried over anhydrous sodium sulphate and concentrated. The residue is distilled under pump vacuum. A colourless oil is obtained. Y=86%. .sup.1 H NMR (CDCl.sub.3): 1.26 (bs, 2H, --NH.sub.2), 1.43-1.66 (m, 4H, --H.sub.2 C--CH.sub.2 --), 2.44-2.51 (t, 2H, --CH.sub.2 --) 2.59 (b s, 2H, --CH.sub.2 --), 2.68-2.76 (m, 4H, --CH.sub.2 --CH.sub.2 --) 3.15-3.19 (d, 2H, --CH.sub.2 --), 3.72-3.78 (q, 2H, --CH.sub.2 --), 6.06 (q, 1H, --CH.dbd.), 7.22-7.41 (m, 5H, phe). .sup.13 C NMR (CDCl.sub.3): 24.6 (--CH.sub.2 --CH.sub.2 --CH.sub.2 --NH.sub.2), 28.1 (--CH.sub.2 --CH.sub.2 --NH.sub.2), 31.9 (--CH.sub.2 --CH.sub.2 --N<, pyrid), 42.2 (--CH.sub.2 --NH.sub.2), 50.4 (--CH.sub.2 --CH.sub.2 --N<, pyrid), 53.3 (.dbd.CH--CH.sub.2 --N<), 58.3 (>N--CH.sub.2 --), 121.9 (>CH--), 124.9 (>CH).sub.2 --), 126.9 (>(CH).sub.2 --), 128.2 (<C.dbd.CH--, pyrid), 135.0 (>C.dbd.CH--, pyrid), 140.9 (>C<).

Example 3

Preparation of N-[4-(4-phenylpiperidinyl)butyl]-2-naphthamide (Do 912)

120 mg of N-[4-(4-phenyl-1,2,3,6-tetrahydropyridinyl)butyl]-2-naphthamide obtained according to Example 2 are dissolved in 20 ml of methanol in a 100 ml Parr bottle. A spatula tip of Pd/C (palladium-on-charcoal) is added and hydrogenation is carried out with the Parr apparatus for 6 hours under a pressure of 60 p.s.i. The catalyst is filtered off and rinsed with methanol and the filtrate is concentrated. Purification is carried out by chromatography on a silica column (eluent: ethyl acetate/methanol 90/10). Crystallization is carried out from hexane. 110 mg of white crystals are obtained. Y=91%. M.p.=143-144.degree. C. .sup.1 H NMR (CDCl.sub.3, 330.degree. K): 1.76-1.86 (m, 7H, --H.sub.2 C--CH.sub.2 --CH.sub.2 --CH<), 2.06-2.14 (m, 2H, --CH.sub.2 --), 2.48-2.54 (m, 4H, --H.sub.2 C--CH.sub.2 --), 3.07-3.13 (m, 2H,--CH.sub.2 --), 3.56-3.60 (q, 2H, --CH.sub.2 --), 6.94 (b.s., 1H, --NH), 7.12-7.29 (m, 5H, >(CH).sub.5 --, phenyl), 7.51-7.55 (m, 2H, >HC--CH<), 7.84-7.93 (m, 4H, >HC--CH--CH--CH<), 8.30 (s, 1H, >CH--).

Analysis C.sub.26 H.sub.30 N.sub.2 O; Calc. % C 80.79, % H 7.82, % N 7.25 Fd. % C 80.66, % H 7.89, % N 7.22

Example 4

Preparation of N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-l-methoxy-4-cyano-2-naphthanid e (883)

120 mg of 1-methoxy-4-cyanonaphthalene-2-carboxylic acid (prepared as in Example 1a)) are dissolved in 20 ml of anhydrous acetone. 2.5 equivalents of triethylamine are added and the mixture is cooled to -15.degree. C. by means of a dry ice/acetone bath. 1.05 equivalents of isobutyl chloroformate are added and reaction is allowed to take place for 1 hour at -15.degree. C. 1.05 equivalents of N-(4-aminobutyl)--N'-(2-methoxyphenyl)piperazine (prepared as in Example 1b)) are then added and reaction is

allowed to take place for 2 hours at room temperature under an inert atmosphere. The triethylamine hydrochloride is filtered off and the filtrate is evaporated to dryness. The evaporation residue is taken up in a small amount of ethyl acetate and the naphthamide is purified by chromatography on a silica column (eluent: ethyl acetate/methanol 90/10). The naphthamide is crystallized from diethyl ether. 76 mg of white crystals are obtained. Y=23%. M.p.=128.degree. C. .sup.13 C NMR (CDCl.sub.3): 24.4 (--CH.sub.2 --CH.sub.2 --CH.sub.2 NH--), 27.5 (--CH.sub.2 --CH.sub.2 --NH--), 39.9 (CH.sub.2 --NH--), 50.4 (--CH.sub.2 --N--(CH.sub.2).sub.2 --), 53.3 (>C--N--(CH.sub.2).sub.2 --); 55.1 (--OCH.sub.3, phenyl), 58.0 (>N--CH.sub.2 --), 63.4 (--OCH.sub.3, naphthyl), 106.7 (--CH--C.tbd.N, .alpha.), 111.0 (--CH--C--OCH.sub.3, phenyl), 116.9 (--C.tbd.N), 117.9 (--CH--CH--C--OCH.sub.3, phenyl), 120.8 (--CH--C--N<, phenyl), 122.5 (>C--C.dbd.O, .beta.), 122.8 (--CH--CH--C--N<, phenyl), 123.6 (--CH--CH--C--C--OCH.sub.3, .beta.), 125.5 (--CH--C--C--OCH.sub.3, .alpha.), 127.5 (--C--C--OCH.sub.3, .gamma.), 128.0 (--CH--C--C--.tbd.N, .alpha.), 130.1 (--CH--C--C.dbd.O, .beta.), 134.4 (--CH--CH--C--C--C.tbd.--N, .beta.), 134.7 (--C--C.tbd.--N, .gamma.), 141.1 (>C--N<, phenyl), 152.1 (--C--OCH3, phenyl), 158.4 (--C--OCH.sub.3, .alpha.), 163.8 (>C.dbd.O).

Example 5

N-[4- (4-(2-Methoxyphenyl)piperazinyl)butyl]-2-naphthamide

M.p.=121.degree. C., C.sub.26 H.sub.31 N.sub.3 O.sub.2 (DO 897)

Example 6

N-[4-(4-(2--Chlorophenyl)piperazinyl)butyl]-3-methoxy-2-naphthamide

M.p.=86.degree. C., C.sub.26 H.sub.30 N.sub.3 O.sub.2 Cl (DO 917)

Example 7

N-[4-(4-(2--Chlorophenyl)piperazinyl)butyl]-2-naphthamide

M.p.=107-109.degree. C., C.sub.25 H.sub.28 ClN.sub.3 O (DO 910)

Example 8

N-[4-(4-(3--Chlorophenyl)piperazinyl)butyl]-2-naphthamide

M.p.=150-152.degree. C., C.sub.25 H.sub.28 ClN.sub.3 O (DO 908)

Example 9

N-[4-(4-(Phenylpiperazinyl)butyl]-2-naphthamide

M.p.=164.degree. C., C.sub.25 H.sub.29 N.sub.3 O (DO 905)

Example 10

N-[4-(4-(2-Methoxyphenyl)piperazinyl)butyl]-1-methoxy-2-naphthamide oxalate

M.p.=164.degree. C., C.sub.27 H.sub.34 N.sub.3 O.sub.3. C.sub.2 H.sub.2 O.sub.4 (897a)

BIOLOGICAL ACTIVITY

The activity of the derivatives of formula (I) according to the invention was evaluated with respect to cells expressing human recombinant dopaminergic receptors, the degree of stimulation of which can be determined by measuring the incorporation of [.sup.3 H]-thymidine: CHO cells expressing the D.sub.2s receptor and NG 108-15 cells expressing the D.sub.3 receptor (Pilon et al., Eur. J. Pharmacol. Mol. Pharmacol. Sect., 1994, 268: 129-139; Sautel et. al. Neuroreport, 1995, 6: 329-332).

Among these derivatives, some exhibit a much greater affinity for the D.sub.3 receptor in comparison with the D.sub.2 receptor.

Whereas compounds of the nafadotride type (above-mentioned French Patent Application No. 91 13103) behave as pure antagonists of the D.sub.3 receptor, the Inventors have discovered that, unexpectedly, the compounds of the present invention behave as powerful partial agonists of dopamine at the D.sub.3 receptor, their intrinsic activity varying between 50% and 80% (dopamine=100%). Thus it is that the compound of Example 5 exhibits an intrinsic activity of 60% and that its 50% effective concentration is 3 nM. This same compound exhibits an apparent affinity with respect to the D.sub.2 receptor which is 25 times smaller than with respect to the D.sub.3 receptor: it consequently constitutes a very selective (partial) agonist of the latter.

What is more, the Inventors have also shown that minimum structural differences among the compounds described here can result in significant variations in the selectivity and the intrinsic activity of the molecules.

For example, when R.sub.3 and R.sub.4 each represent a methoxy group, this disubstitution causes the D.sub.3 receptor/D.sub.2 receptor selectivity to be lost, in comparison with a monosubstitution. Moreover, the presence of a chlorine substituent (R.sub.3 or R.sub.4) greatly decreases the affinity of the derivative (I) for the D.sub.3 receptor.

These properties lead to therapeutic applications which cannot yet be envisaged with existing dopaminergic agents. In fact, the high selectivity of the molecules allows selective activation of the dopaminergic transmissions of the limbic regions involved in emotional and cognitive processes (which express the D.sub.3 receptor), without interference with the dopaminergic transmissions of the extra-pyramidal, antehypophysial or vegetative (area postrema) systems. They should therefore prevent the side effects of

the existing compounds, related to the effect of the latter on the extrapyramidal, antehypophysial and vegetative areas. In addition, the D.sub.3 partial agonist nature is such as to normalize the dopaminergic transmissions without the risk of excessive activation.

The derivatives of the invention can thus be used for the preparation of pharmaceutical compositions and medicaments for the treatment of neuropsychiatric conditions involving the D.sub.3 receptor, such as psychotic or depressive states.

In addition, taking into account the role of the D.sub.3 receptor in drug-dependence states, pharmaceutical compositions or medicaments based on these derivatives can be usefully administered in states related to abstinence and/or facilitate detoxification of subjects dependent on cocaine, heroin, alcohol, nicotine, and the like.

The derivatives according to the invention also have effects on penile erection and can also be used for the preparation of pharmaceutical compositions and medicaments for the treatment of disorders of a sexual nature, in particular male impotence.

The derivatives according to the invention, as well as, generally, agonists of the D.sub.3 receptor, can also be used for a treatment complementary to the treatment of Parkinson's disease by L-DOPA. The invention thus relates to such complementary medicaments as well as to the use of agonists of the D.sub.3 receptor, including the novel products of the present invention, for the preparation of a medicament for the complementary treatment of Parkinson's disease.

This activity could be explained by the discovery, with respect to an animal model of Parkinson's disease, that the treatment by L-DOPA induces the expression, in-the cells of the striatum, of D.sub.3 receptors which would underline the sensitization to the motor effects of L-DOPA.

The derivatives of formula (I) according to the invention can be administered in particular by the oral route in the form of a pharmaceutical composition.

The therapeutically useful doses vary with the various derivatives but, for the compound of Example 5, it may be specified that they lie between 0.05 and 5 mg/kg by the oral route.

United States Patent **5,994,391**
Lee , et al. **November 30, 1999**

Benzothiepines having activity as inhibitors of ileal bile acid transport and taurocholate uptake

Abstract

Provided are novel benzothiepines, derivatives, and analogs thereof; pharmaceutical compositions containing them; and methods of using these compounds and compositions in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia, in mammals.

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OR.sup.13, NR.sup.13 R.sup.14, SR.sup.13, S(O)R.sup.13, SO.sub.2 R.sup.13, SO.sub.3 R.sup.13, NR.sup.13 OR.sup.14, NR.sup.13 NR.sup.14 R.sup.15, NO.sub.2, CO.sub.2 R.sup.13, CN, OM, SO.sub.2 OM, SO.sub.2 NR.sup.13 R.sup.14, C(O)NR.sup.13 R.sup.14, C(O)OM, COR.sup.13, P(O)R.sup.13 R.sup.14, P.sup.+ R.sup.13 R.sup.14 R.sup.15 A.sup.-, P(OR.sup.13)OR.sup.14, S.sup.+ R.sup.13 R.sup.14 A.sup.-, and N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-.

313. The process of claim 312 wherein the cyclic sulfate has the formula: ##STR558## and the thiophenol has the formula: ##STR559## wherein R.sup.1, R.sup.2, R.sup.5, R.sup.x and q are as defined in claim 312.

314. The process of claim 313 wherein the R.sup.1 and R.sup.2 are alkyl.

315. The process of claim 313 wherein the R.sup.1 and R.sup.2 are selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

316. The process of claim 313 wherein the R.sup.1 and R.sup.2 are n-butyl.

317. The process of claim 313 wherein the alcohol is oxidized with an oxidizing agent to form an aldehyde.

318. The process of claim 317 wherein the aldehyde is oxidized with an oxidizing agent to form a sulfone-aldehyde.

319. The process of claim 313 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is a base having a pH between about 8 to about 9.

320. The process of claim 313 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is an alkali alkoxide base.

321. The process of claim 313 wherein the sulfone-aldehyde is cyclized with potassium tert-butoxide.

322. The process of claim 313 wherein the alcohol is oxidized with pyridinium chlorochromate to form an aldehyde; the aldehyde is oxidized with metachloroperbenzoic acid to form a sulfone-aldehyde; and the sulfone-aldehyde is cyclized with potassium tert-butoxide.

323. A process for the preparation of a compound having the formula LI: ##STR560## comprising: treating a halobenzene with an abstracting agent;

coupling the halobenzene and a cyclic sulfate to form an intermediate comprising a sulfate group; and

removing the sulfate group of the intermediate to form the compound of formula LI; wherein

q is an integer from 1 to 4;

R.sup.1 and R.sup.2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR.sup.9, NR.sup.9 R.sup.10, N.sup.+ R.sup.9 R.sup.10 R.sup.w A.sup.-, SR.sup.9, S.sup.+ R.sup.9 R.sup.10 A.sup.-, P.sup.+ R.sup.9 R.sup.10 R.sup.11 A.sup.-, S(O)R.sup.9, SO.sub.2 R.sup.9, SO.sub.3 R.sup.9, CO.sub.2 R.sup.9, CN, halogen, oxo, and CONR.sup.9 R.sup.10,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR.sup.9,

N.sup.+ R.sup.9 R.sup.10 A.sup.-, S, SO, SO.sub.2, S.sup.+ R.sup.9 A.sup.-, P.sup.+ R.sup.9 R.sup.10 A.sup.-, or phenylene,

wherein R.sup.9, R.sup.10, and R.sup.w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R.sup.1 and R.sup.2 taken together with the carbon to which they are attached form C.sub.3 -C.sub.10 cycloalkyl;

R.sup.3 is hydroxy;

R.sup.4 is hydrogen;

R.sup.5 and R.sup.6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR.sup.30, SR.sup.9, S(O)R.sup.9, SO.sub.2 R.sup.9, and SO.sub.3 R.sup.9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR.sup.13, NR.sup.13 R.sup.14, SR.sup.13, S(O)R.sup.13, SO.sub.2 R.sup.13, SO.sub.3 R.sup.13, NR.sup.13 OR.sup.14, NR.sup.13 NR.sup.14 R.sup.15, NO.sub.2, CO.sub.2 R.sup.13, CN, OM, SO.sub.2 OM, SO.sub.2 NR.sup.13 R.sup.14, C(O)NR.sup.13 R.sup.14, C(O)OM, CR.sup.13, NR.sup.13 C(O)R.sup.14, NR.sup.13 C(O)NR.sup.14 R.sup.15, NR.sup.13 CO.sub.2 R.sup.14,

OC(O)R.sup.13, OC(O)NR.sup.13 R.sup.14, NR.sup.13 SOR.sup.14, NR.sup.13 SO.sub.2 R.sup.14, NR.sup.13 SONR.sup.14 R.sup.15, NR.sup.13 SO.sub.2 NR.sup.14 R.sup.15, P(O)R.sup.13 R.sup.14, P.sup.+ R.sup.13 R.sup.14 R.sup.15 A.sup.-, P(OR.sup.13)OR.sup.14, S.sup.+ R.sup.13 R.sup.14 A.sup.-, and N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-,

wherein:

A.sup.- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR.sup.7, NR.sup.7 R.sup.8, SR.sup.7, S(O)R.sup.7, SO.sub.2 R.sup.7, SO.sub.3 R.sup.7, CO.sub.2 R.sup.7, CN, oxo, CONR.sup.7 R.sup.8, N.sup.+ R.sup.7 R.sup.8 R.sup.9 A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(O)R.sup.7 R.sup.8, P.sup.+ R.sup.7 R.sup.8 R.sup.9 A.sup.-, and P(O)(OR.sup.7)OR.sup.8, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR.sup.7, N.sup.+ R.sup.7 R.sup.8 A-, S, SO, SO.sub.2, S.sup.+ R.sup.7 A-, PR.sup.7, P(O)R.sup.7, P.sup.+ R.sup.7 R.sup.8 A-, or phenylene, and R.sup.13, R.sup.14, and R.sup.15 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR.sup.9, N.sup.+ R.sup.9 R.sup.10 A-, S, SO, SO.sub.2, S.sup.+ R.sup.9 A.sup.-, PR.sup.9, P.sup.+ R.sup.9 R.sup.10 A-, P(O)R.sup.9, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R.sup.13, R.sup.14, and R.sup.15 are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, OR.sup.9, NR.sup.9 R.sup.10, N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-, SR.sup.9, S(O)R.sup.9, SO.sub.2 R.sup.9, SO.sub.3 R.sup.9, oxo, CO.sub.2 R.sup.9, CN, halogen, CONR.sup.9 R.sup.10, SO.sub.2 OM, SO.sub.2 NR.sup.9 R.sup.10, PO(OR.sup.16)OR.sup.17, P.sup.+ R.sup.9 R.sup.10 R.sup.11 A-, S.sup.+ R.sup.9 R.sup.10 A-, and C(O)OM,

wherein R.sup.16 and R.sup.17 are independently selected from the substituents constituting R.sup.9 and M; or

R.sup.13 and R.sup.14, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R.sup.14 and R.sup.15, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R.sup.30 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R.sup.7 and R.sup.8 are hydrogen; and

one or more R.sup.x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR.sup.13, NR.sup.13 R.sup.14, SR.sup.13, S(O)R.sup.13, S(O).sub.2 R.sup.13, SO.sub.3 R.sup.13, S.sup.+ R.sup.13 R.sup.14 A.sup.-, NR.sup.13 OR.sup.14, NR.sup.13 NR.sup.14 R.sup.15, NO.sub.2, CO.sub.2 R.sup.13, CN, OM, SO.sub.2 OM, SO.sub.2 NR.sup.13 R.sup.14, NR.sup.14 C(O)R.sup.13, C(O)NR.sup.13 R.sup.14, NR.sup.14 C(O)R.sup.13, C(O)OM, COR.sup.13, OR.sup.18, S(O).sub.n NR.sup.18, NR.sup.13 R.sup.18, NR.sup.18 OR.sup.14, N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-, P.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR.sup.9, NR.sup.9 R.sup.10, N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-, SR.sup.9, S(O)R.sup.9, SO.sub.2 R, SO.sub.3 R.sup.9, oxo, CO.sub.2 R.sup.9, CN, halogen, CONR.sup.9 R.sup.10, SO.sub.2 OM, SO.sub.2 NR.sup.9 R.sup.10, PO(OR.sup.16)OR.sup.17, P.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-, S.sup.+ R.sup.9 R.sup.10 A.sup.-, or C(O)OM, and

wherein R.sup.18 is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR.sup.9, NR.sup.9 R.sup.10, N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.-, SR.sup.9, S(O)R.sup.9, SO.sub.2 R.sup.9, SO.sub.3 R.sup.9, oxo, CO.sub.2 R.sup.9, CN, halogen, CONR.sup.9 R.sup.10, SO.sub.3 R.sup.9, SO.sub.2 OM, SO.sub.2 NR.sup.9 R.sup.10, PO(OR.sup.16)OR.sup.17, and C(O)OM,

wherein in R.sup.x, one or more carbons are optionally replaced by O, NR.sup.13, N.sup.+ R.sup.13 R.sup.14 A.sup.-, S, SO, SO.sub.2, S.sup.+ R.sup.13 A.sup.-,

PR.sup.13, P(O)R.sup.13, P.sup.+ R.sup.13 R.sup.14 A.sup.-, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR.sup.9, N.sup.+ R.sup.9 R.sup.10 A.sup.-, S, SO, SO.sub.2, S.sup.+ R.sup.9 A.sup.-, PR.sup.9, P.sup.+ R.sup.9 R.sup.10 A.sup.-, or P(O)R.sup.9 ;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR.sup.13, NR.sup.13 R.sup.14, SR.sup.13, S(O)R.sup.13, SO.sub.2 R.sup.13, SO.sub.3 R.sup.13, NR.sup.13 OR.sup.14, NR.sup.13 NR.sup.14 R.sup.15, NO.sub.2, CO.sub.2 R.sup.13, CN, OM, SO.sub.2 OM, SO.sub.2 NR.sup.13 R.sup.14, C(O)NR.sup.13 R.sup.14, C(O)OM, COR.sup.13, P(O)R.sup.13 R.sup.14, P.sup.+ R.sup.13 R.sup.14 R.sup.15 A.sup.-, P(OR.sup.13)OR.sup.14, S.sup.+ R.sup.13 R.sup.14 A.sup.-, and N.sup.+ R.sup.9 R.sup.11 R.sup.12 A.sup.- ; and

R.sup.e is an ***electron-withdrawing group*** located at the para or ortho position.

324. The process of claim 323 wherein the cyclic sulfate has the formula: ##STR561## and the halobenzene has the formula: ##STR562## wherein R.sup.h is halogen, and R.sup.1, R.sup.2, R.sup.5, R.sup.x, R.sup.e and q are as defined in claim 323.

325. The process of claim 324 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.

326. The process of claim 325 wherein the hydrolyzing agent is a mineral acid.

327. The process of claim 325 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.

328. The process of claim 324 wherein the abstracting agent is a dialkali metal sulfide.

329. The process of claim 324 wherein the abstracting agent is dilithium sulfide.

330. The process of claim 324 wherein R.sup.1 and R.sup.2 are alkyl.

331. The process of claim 324 wherein R.sup.1 and R.sup.2 are selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

332. The process of claim 324 wherein R.sup.1 and R.sup.2 are n-butyl.

333. The process of claim 324 wherein R.sup.h is chloro.

334. The process of claim 324 wherein R.sup.e is p-nitro.